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Treatment of Benign Cold Thyroid Nodules: A Randomized Clinical Trial of Percutaneous Laser Ablation Versus Levothyroxine Therapy or Follow-up

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Aim of the study. To compare clinical and ultrasound (US) changes induced in cold thyroid nodules by US-guided percutaneous laser ablation (PLA) versus follow-up or levothyroxine (LT4) suppressive therapy. *Methods:* 62 patients randomly assigned to a single PLA (Group 1), LT4 (Group 2), or follow-up (Group 3). *Entry criteria*: euthyroid patients with a solid thyroid nodule >5 mL and benign cytological findings. *Treatment*: Group 1: PLA was performed with a 1.064 μm neodymium yttrium-aluminum-garnet laser with output power of 3 W for 10 minutes; Group 2: the LT4 dose was adjusted to induce thyrotropin suppression; Group 3: no treatment. *Results.* In Group 1 a significant nodule reduction was found 6 and 12 months after PLA (delta volume: $-42.7 \pm 13.6\%$; $p = 0.001$). A reduction >50% was found in 33.3% of cases. In Group 2 a nonsignificant nodule shrinkage was observed. A nonsignificant volume increase was observed in Group 3. Improvement of local symptoms was registered in 81.2% of patients in Group 1 vs. 13.3% in Group 2 and 0.0% in Group 3 ($p = 0.001$). No complications were noted. *Conclusions.* A single PLA induced significant volume reduction and improvement of local symptoms. PLA was more effective than LT4. Follow-up was associated with nodule growth and progression of local symptoms. PLA should be considered a potential mini-invasive alternative to surgery in symptomatic patients with benign cold thyroid nodules.

Introduction

The combined use of sonographic criteria (US) and fine-needle aspiration biopsy (FNA) has greatly reduced the need for diagnostic thyroidectomy; only a small percentage of nodules currently require surgery (1–6).

Solid thyroid nodules with benign cytology usually go to long-term follow-up (1–4); some are treated with thyrotropin (TSH)-suppressive levothyroxine (LT4) therapy. The use of LT4 in thyroid nodules has shown controversial results (7–9) and many conditions (old age, menopause, cardiovascular disease, osteoporosis) represent a contraindication to long-term LT4 therapy (10–12). Hence, benign cold thyroid nodules are frequently followed up over time with clinical and US surveillance. However, a variable proportion of these lesions present slow but progressive growth (8,9), induce patient concern or local pressure symptoms, and are eventually dealt with surgically (1,2).

Surgery is a well-established and effective therapy for thyroid lesions that cause pressure symptoms (1,2,4), but a few patients present a high surgical risk due to advanced age or respiratory or cardiovascular disease. Moreover, surgical treatment is expensive, presents a low but well-defined risk of temporary or permanent complications, and may induce cosmetic problems (13).

Preliminary studies (14) with surgically removed thyroid glands and with patients not eligible for, or refusing, surgical treatment have tested percutaneous laser thermal ablation (PLA) as a minimally invasive US-guided debulking procedure. PLA has been reported to be a safe and rapid outpatient procedure, effective in reducing the volume of large cold and hot thyroid nodules (15,16).

The aim of this prospective randomized trial was to compare the 12-month changes in nodule volume and local symptoms induced by a single PLA session with those induced by long-term LT4 suppressive therapy in a series of benign large cold thyroid nodules and then to compare the findings in the two groups with the natural history of a series of thyroid nodules followed by means of clinical surveillance with no active treatment.

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Materials and Methods

Patients

Entry criteria were: a) presence of a single or dominant palpable nodule, either solid or with a small fluid component (less than 20% at US examination), with volume greater than 5 mL, and with at least one diameter greater than 30 mm; b) hypoactive appearance at ^{99m}Tc thyroid scintiscan; c) benign cytology at two consecutive US-guided FNA biopsies (17); d) free thyroid hormones, TSH, and antithyroid antibodies within normal range; e) age between 18 and 60 years; f) refusal of or ineligibility for surgery; g) untreated thyroid disease.

Between January 2003 and June 2004 about 2500 patients with thyroid disease were referred to the outpatient clinic of our department (Fig. 1). Eighty-six patients with cold thyroid nodules matching the entry criteria were considered suitable for the study. No patient had previously undergone surgery, radioiodine, or LT4 treatment for thyroid disease. All the patients lived in the greater Rome metropolitan area, a borderline iodine-deficient area (median daily urinary iodine excretion: 92 μg).

After being fully informed, 62 of the 86 eligible patients (age range 28–58 years; mean, 46.2 $\pm$ 7.0 years, 7 [11.3%] males and 55 [88.7%] females) gave their written consent and entered the study.

Patients were randomly assigned to a single session of PLA (Group 1), a 12-month LT4 treatment (Group 2), or follow-up alone (Group 3). A computer-based number generator was used to randomly assign each patient to one of the three groups.

The study was conducted in compliance with the Helsinki Declaration and the local Bioethics Committee.

Nodule volume assessment

Sonographic evaluation was conducted at baseline and after 1, 6, and 12 months by means of a commercially available US scanner (Tecnos MPX, Esaote, Genoa, Italy), equipped with a 7.5–13.0 Mhz linear transducer. The nodule volume was calculated with the ellipsoid formula (diameter 1$\times$diameter 2$\times$ diameter 3$\times$0.52) by two experienced sonographers. The previously defined intra- and inter-observer coefficients of variation for sonographic volume assessment were 3.9% and 5.6% respectively.

Laboratory evaluation

Serum TSH, free thyroid hormones, thyroglobulin (Tg), and thyroid antibodies were assessed at baseline and again at 1, 6, and 12 months.

TSH (normal range 0.2–4.0 μIU/mL) and Tg (normal range 0.2–50.0 ng/mL) levels were determined with a commercially available immunoradiometric assay (Sorin Biomedica, Saluggia, Italy). Serum levels of free triiodothyronine (FT3, normal range 2.2–5.0 pg/mL), thyroxine (FT4, normal range 8.0–18.5 pg/mL), anti-thyroglobulin antibodies (TgAb, normal range 0.0–70.0 IU/mL), anti-thyroid peroxidase antibodies (TPOAb, normal range 0.0–70.0 IU/mL), and calcitonin (normal values $<$10 ng/mL) were determined with commercially available radioimmunologic assay kits (Radim, Pomezia, Italy).

Treatments

Group 1: percutaneous laser ablation. Both evaluation of the thyroid gland and sonographic guidance for PLA treatment were performed with the same US scanner equipped with a 7.5–13.0 Mhz linear transducer. Two 75 mm, 21-gauge spinal needles (Becton-Dickinson, Rutherford, NJ) were inserted into the thyroid lesions under US monitoring. In a single patient who had a thyroid nodule volume greater than 20 ml PLA was performed with four needles. The needle tips were introduced into the nodules along their longest axis, and the needle positions were confirmed with two-plane US images. Care was taken to maintain a safety distance of 10 mm between the needle tips and the surrounding cervical structures and to leave interneedle spacing of 1.0 cm. A 300 μm plane-cut quartz optical fiber (Medical Energy, Inc., Pensacola, FL) was inserted through the sheath of the needles, which were then withdrawn 5 mm, leaving the fiber tips in direct contact with the tissue. The energy source, a continuous-wave neodymium yttrium-aluminum-garnet (Nd-YAG) laser operating at 1.064 μm (D.E.K.A.-M.E.L.A.; Florence, Italy), was used with an optical beam-splitting device (Smart 1064 HCC; D.E.K.A.-M.E.L.A.; Florence, Italy). Laser illuminations were monitored continuously with real-time US.

In six patients with lesions under 15 mL PLA was performed with a single illumination; in 14 patients with nodules whose volume exceeded 15 mL, in order to enlarge the coagulation necrosis along the longitudinal axis, two consecutive illuminations were performed during the same session withdrawing both the needles and the laser fibers 10 mm for the second illumination (16). In one patient with a nodule volume greater than 20 mL PLA was performed with four needles and two illuminations during the same treatment.

Laser energy was delivered in all cases with an output power of 3 W and an illumination period of 10 minutes, reaching a total energy delivery of 1800 J per fiber per treatment. Thus, on the basis of their baseline volume, the total amount of energy delivered to the nodules during an entire treatment session ranged from 3600 to 14,400 J. The mean energy delivery was 1221 $\pm$ 679 J/mL of thyroid nodule tissue (median 1054 J/mL).

At the end of the PLA session the optical fibers were gradually withdrawn with the laser kept off. Subsequent US scans were performed to reveal intra- or extraglandular complications and the patients were monitored for 60 minutes in the outpatient clinic.

Immediately before PLA, patients were given an intramuscular injection of betamethasone (Bentelan 4 mg, Biofutura Pharma, Italy). Patients complaining of persistent cervical pain were given ketoprofen (Orudis Retard, 200 mg tablets, Aventis Pharma, Italy) for two days.

Group 2: LT4 treatment. A standard dose of LT4 (Eutirox, Bracco, Italy, 1.5 μg/kg of weight daily) was administered to the patients assigned to LT4 treatment. A modification of the dose was scheduled at day 35 of a run-in period, on the basis of TSH levels. LT4 was increased if TSH levels $>$0.30 μIU/mL and was decreased in the case of undetectable TSH with FT3 increase or if persistent nervousness, tremors, or tachycardia appeared.

Group 3: Follow-up. Patients followed the same schedule for clinical, hormonal, and US check-ups as did the two active treatment groups.

Assessment of local symptoms

The baseline and final assessments of local symptoms were conducted by means of questionnaires specifically developed but not validated. These questionnaires were completed anonymously by patients before and at the end of the 12-month period of treatment or follow-up.

Scoring for baseline and final symptoms: 0 = no symptoms; 1 = presence of local symptoms (cosmetic complaints, cervical constriction, dyspnoea or dysphagia).

Symptom change score: 0 = symptoms unchanged vs baseline; +1 = worsening of symptoms; −1 = improvement or disappearance of symptoms.

In Group 1, tolerability of PLA treatment was assessed by asking patients for their consent to a second laser ablation, if needed.

Statistical analysis

The primary hypothesis of this study was that patients treated with PLA had a volume change in their thyroid nodules similar to that of patients treated with LT4 or with no active therapy (null hypothesis). The mean baseline and final volumes in the three groups were compared by Student *t* test for unpaired data. The secondary hypothesis was that the nodule volume variation within each group presented no difference. The mean baseline and final volumes within each group were compared by Student *t* test for paired data and the nodule volume changes of each group were evaluated by Student *t* test for unpaired data. The symptom modifications registered in the three groups were evaluated by χ^2 test. Hormonal and autoantibody changes were compared and analyzed by ANOVA test. Drop-outs were registered and their number and distribution within the three groups were analyzed by χ^2 test.

Statistical analyses were performed according to the intention-to-treat principle. Differences were considered significant when $p < 0.05$. Data were analyzed using SPSS for Windows (version 13.0, SPSS Inc, Chicago, IL).

Results

The baseline characteristics of the 62 enrolled patients are shown in Table 1. No significant differences in the mean baseline features were found between the three groups.

Nodule volume

Group 1. In the PLA-treated group a significant nodule volume reduction (-5.2 ± 3.1 mL) was found at the 12-month US assessment, and at the end of the study a nodule volume reduction >50% was observed in 7/21 patients (33.3%). A significant correlation ($r^2 = 0.69$) between the amount of energy delivered and the volume of tissue ablated was observed.

Group 2. The LT4-treated patients showed a slight (-0.6 ± 2.3 mL), nonsignificant, nodule volume decrease after 12 months of therapy. None of the patients in this group presented a reduction of nodule volume greater than 50% versus the baseline value.

Group 3. The follow-up group showed a nonsignificant increase ($+0.7 \pm 2.2$ mL) in nodule volume after 12 months. None of the patients in this group presented a reduction in nodule volume greater than 50% versus the baseline value.

Comparison of the three groups

At the end of the study a significant difference in nodule volume was observed in the PLA group in contradistinction to both the LT4-treatment (6.6 ± 2.7 vs. 12.8 ± 5.5 mL, $p < 0.01$) and the follow-up groups (6.6 ± 2.7 mL vs. 13.9 ± 7.1 mL; $p < 0.001$). A 12-month nodule volume reduction >50% was found in 7/21 patients (33%) in Group 1 versus 0/21 patients (0.0%) in both Groups 2 and 3 ($p < 0.001$). No significant difference in final volume was observed between the LT4 group and the follow-up group (12.9 ± 7.5 vs. 12.8 ± 5.5 mL; p = NS). A comparison of the changes observed in the three groups is summarized in Table 2.

Hormonal profile

Group 1. An increase in serum TgAb antibodies (>70 IU/mL) was registered in two cases (9.5%) at the 6-month follow-up visit and was confirmed at 12 months. No significant changes were observed in serum TSH, free thyroid hormones, TPOAb, or calcitonin levels.

Group 2. The initial LT4 dosage was increased in 7/21 patients (33.3%) and decreased in 2/21 patients (9.5%) on the basis of the serum TSH value at day 35 of the run-in phase.

Table 1. Baseline Features of the Three Groups of Patients[a]

	PLA group	*LT4 group*	*Follow-up group*	p *value*
Number	21	21	20	NS
Age (yr)	44.9 ± 5.1	46.5 ± 8.2	47.1 ± 7.7	NS
Female/male ratio (odds)	(18:3) = 6	(19:2) = 9.5	(18:2) = 9	NS
Nodule volume (mL)	11.7 ± 5.1	13.6 ± 6.3	12.1 ± 3.9	NS
Local symptoms	76.2% (16/21)	71.4% (15/21)	70.0% (14/20)	NS
TSH (mUI/mL)	1.4 ± 0.6	1.8 ± 0.9	1.7 ± 0.6	NS[b]
FT3 (pg/mL)	3.4 ± 0.6	3.1 ± 0.6	3.2 ± 0.6	NS[b]
FT4 (pg/mL)	13.7 ± 1.8	12.4 ± 1.9	12.5 ± 2.2	NS[b]
Tg (ng/mL)	71.6 ± 33.6	84.1 ± 47.37	69.4 ± 36.7	NS
TPOAb >70 IU/mL (%)	0	0	0	NS[b]
TgAb >70 IU/mL (%)	0	0	0	NS[b]
Calcitonin >10 ng/mL (%)	0	0	0	NS[b]

[a]TSH = thyrotropin; FT3 = free triiodothyronine; FT4 = free thyroxine; Tg = thyroglobulin; TPOAb = thyroid peroxidase antibody; TgAb = thyroglobulin antibody.
[b]All patients were euthyroid and had TgAb, TPOAb, and calcitonin levels within the normal range.

Table 2. Comparison of the Three Groups at the End of the 12-Month Study[a]

	PLA group	*LT4 group*	*Follow-up group*	p *value*
Nodule volume (mL)	6.2 ± 2.7	12.9 ± 7.4	12.8 ± 5.5	0.001[b]
Delta volume (mL)	-5.2 ± 3.1	-0.6 ± 2.2	$+0.7 \pm 2.2$	<0.001[b] <0.03[c]
Nodule volume decrease >50% (%)	33.3 (7/21)	0.0 (0/21)	0.0 (0/20)	<0.01[b]
Worsening of symptoms (%)	0.0 (0/21)	4.8 (1/21)	45.0 (9/20)	<0.001[d]
Improvement of symptoms (%)	81.2 (13/16)	13.3 (2/15)	0.0 (0/14)	<0.001[c]
Still symptomatic patients (%)	47.6 (10/21)	76.2 (16/21)	90.0 (18/20)	0.001[e]
TSH (mIU/mL)	1.6 ± 0.7	0.17 ± 0.1	1.6 ± 0.5	<0.01[e]
FT3 (pg/mL)	3.2 ± 0.7	3.0 ± 0.4	3.2 ± 0.4	NS
FT4 (pg/mL)	13.4 ± 4.2	16.7 ± 1.3	12.8 ± 2.1	0.06[e]
Tg (ng/mL)	87.8 ± 31.5	75.5 ± 39.5	80.3 ± 31	NS
TPOAb >70 IU/mL (%)	0	0	0	NS
TgAb >70 IU/mL (%)	9.5 (2/21)	0	0	NS
Calcitonin >10 ng/mL (%)	0	0	0	NS

[a]PLA = percutaneous laser ablation; LT4 = levothyroxine; TSH = thryotropin; FT3 = free triiodothyronine; FT4 = free thyroxine; Tg = thyroglobulin; TPOAb = thyroid peroxidase antibody; TgAb = thyroglobulin antibody.
[b]PLA group vs. LT4 and follow-up groups.
[c]LT4 group vs. follow-up group.
[d]Follow-up group vs. PLA and LT4 groups.
[e]LT4 group vs. PLA and follow-up groups.

The TSH levels were undetectable or at the lower limit of the normal range in 21/21 patients (100%) at both the 6- and the 12-month follow-up visits. The final FT4 values exceeded the normal range in 3/21 patients (14.3%), with normal values of FT3 in all cases. No significant modifications were observed in Tg, antithyroid antibodies, or calcitonin levels.

Group 3. No significant modifications were observed in plasma levels of TSH, Tg, free thyroid hormones, antithyroid antibodies, or calcitonin.

Changes in local symptoms

Group 1. Of the PLA-treated patients, 13/16 (81.2% of cases) reported an improvement in or disappearance of local symptoms at 12 months, and none complained of their worsening (symptom score: basal 16/21 vs. final 10/21; $p = \text{NS}$).

Group 2. Of the LT4-treated patients, 2/15 (13.3%) reported an improvement and one a worsening of local symptoms (symptom score: basal 15/21 vs. final 16/21; $p = \text{NS}$).

Group 3. No patient in the follow-up group reported an improvement in cervical symptoms and 8/20 (45.0%) complained of a worsening of local symptoms (symptom score: basal 14/20 vs. final: 18/20; $p = \text{NS}$).

Comparison of the three groups

The prevalence of pressure symptoms and cosmetic problems was similar in all three groups at baseline (76.2%, 71.4%, and 70.0% of cases respectively). At the end of the study, a significant difference in local symptoms was observed in Group 1 compared with both the LT4-treatment and the follow-up groups. Symptom improvement was registered in 81.2% of patients in Group 1 versus 13.3% in Group 2 and 0.0% in Group 3 ($p = 0.001$), while worsening of local symptoms was observed in 45% in Group 3 versus 0.0% in Group 1 and 4.8% in Group 2 ($p = 0.001$).

Side effects and patient compliance

Group 1. All patients but one experienced a mild burning cervical pain during the treatment. The pain was well tolerated and usually ceased as soon as the energy was turned off. In three cases (14.3%) oral ketoprofen was administered during the following 48 hours because of mild but persistent cervical pain. One patient (4.7% of the treated cases) withheld his consent to a possible second PLA treatment, describing the laser ablation procedure as extremely painful.

Group 2. Eight out of 21 (38.1%) patients complained of persistent tachycardia or nervousness, but no one withdrew from the study.

Group 3. One drop-out (5%) was registered in the follow-up group. This patient underwent surgical treatment because of the progressive growth of his nodule and the associated worsening of local symptoms. The histological diagnosis was benign follicular adenoma.

Discussion

Large-volume or progressively growing nodules which are cold on radioisotope scintiscan and which cause local pressure symptoms can be managed nonsurgically by means of TSH-suppressive therapy, mini-invasive US-guided procedures, or follow-up with no active treatment.

As a clinically significant decrease in nodule volume is reported only in a small percentage of patients (about 20% of palpable nodules) treated with LT4, and the growth of many large nodules seems to be only slightly dependent on TSH levels (18,19), US-guided percutaneous ethanol injection (PEI) was proposed in 1990 as a debulking procedure for benign thyroid nodules (20). Although a few papers reported satisfactory results with PEI treatment of solid thyroid nodules, it presents many limitations (21–23). Hence PEI is currently indicated only for the treatment of cystic or predominantly cystic thyroid lesions (1,23,24).

On the basis of a body of experimental and clinical evidence (14,25–27), PLA was proposed for the debulking of large thyroid lesions that are not amenable to radioiodine or surgical treatment (15,16). PLA, in contrast to PEI, induced a fairly predictable area of necrosis, reducing the risk of side effects and damage to surrounding cervical structures. In a few recent clinical trials, PLA demonstrated a high level of effectiveness and safety (16,28–32). The results of our study can be summarized as follows.

Nodule volume

A single PLA treatment succeeded in inducing a rapid, significant, and persistent reduction in thyroid nodule volume. The mean nodule reduction, expressed as a percentage of the pretreatment volume, was over 40% and confirmed the effects reported by previous studies. The efficacy of PLA is predictable, although within limits, since nearly a third of the PLA-treated nodules presented a volume reduction of about 50%. A significant correlation ($r^2 = 0.69$) between the amount of energy delivered and the volume of tissue ablated was observed, in accordance with the results of previous feasibility (16) and clinical trials (29). In the present study, the total energy delivered per milliliter of thyroid nodule volume was higher than in recent trials performed with continuous-wave infrared diode lasers operating at 820 or 980 nm (33,34). Given the effectiveness of debulking with low energy delivery reported in these studies, a comparative trial evaluating the effects of Nd-YAG versus diode laser seems highly advisable.

LT4 treatment of benign thyroid nodules is controversial (7–9,18,19) and is not currently recommended (1,2). In the present study on large thyroid nodules, neither mean nodule volume nor the number of nodules presenting a dimensional decrease of 50% showed significant changes with LT4.

Most of the thyroid nodules followed up without any treatment presented slow but progressive growth. These data are in accordance with the results of previous controlled trials on solid nodules (8,18) and do not confirm the few studies (4,9) demonstrating a "spontaneous" regression of thyroid nodules, which may have occurred in complex thyroid lesions due to the reabsorption of their fluid component.

Hormonal profile

Our enrollment criteria excluded patients with autoimmune thyroid disease, but after PLA two patients showed persistently high TgAb. However, no change in thyroid function was registered.

The LT4-treated patients presented a steady suppression of their TSH levels, with FT4 values at the upper limit of the normal range.

Thyroid hormonal profiles were quite stable in the follow-up group throughout the observation period.

Local symptoms

Most PLA-treated patients reported a significant symptomatic improvement after 12 months. The prevalence of symptomatic improvement was significantly higher (71% of cases) in PLA-treated patients than in LT4-treated or follow-up patients (9.5% and 0.0% respectively). No patient in Group 1 complained of exacerbated symptoms, in contrast with the LT4-treated and follow-up patients, who complained of the aggravation of local symptoms in 4.8% and 45.0% of cases respectively.

Our data confirm the results of an earlier study that reports a clinically significant reduction of local pressure symptoms and of cosmetic complaints after PLA treatment of cold thyroid nodules (28).

After 12 months about 10% of LT4-treated patients presented symptomatic improvement, despite the only slight decrease in the mean volume of their nodules. In these cases the beneficial effect of TSH suppression on local symptoms was probably due to the shrinkage of the still TSH-dependent perinodular thyroid tissue (18). Total thyroid volume was not systematically assessed during the present study. Hence, the potential beneficial effects of long-term TSH suppression on the growth of the thyroid gland and of small coexistent thyroid nodules in patients with nodular goiter cannot be evaluated.

The design of our trial did not involve the use of imaging tools (like spiral computed tomography or magnetic resonance assessment of the tracheal area) to evaluate the quantitative changes in nodular goiter compression on the surrounding cervical structures. This fact, together with the unblinded design of the trial, makes it impossible to rule out the possibility of a placebo effect skewing the analysis of the changes in subjective symptoms in the treated (Groups 1 and 2) patients.

In patients with large thyroid nodules, follow-up alone was associated with a high probability of further nodule volume increase and of local symptom progression during the next year.

Side effects

As reported in previous studies (14,16,28,29), PLA induced in all patients a burning cervical pain, which rapidly decreased as soon as the energy was turned off. This pain was well tolerated and only 25% of patients complained of persistent cervical discomfort and tenderness. A treatment with ketoprofen tablets controlled pain in all these cases within 48 hours.

No major complication was registered and no patient revealed symptoms of transient thyrotoxicosis. Thus, when correctly performed by experienced operators, PLA proved to be a safe and well-tolerated procedure.

In the LT4-treated group, nearly a quarter of cases complained of persistent and unpleasant symptoms including tachycardia, nervousness, and tremors (18). The long-term side effects of TSH-suppressive therapy (cardiac hypertrophy, atrial arrhythmia, and increased risk of osteoporosis) were not assessed in our study.

No side effects were reported in the follow-up group, but one drop-out was registered. This patient requested surgical treatment because of the progressive growth of his thyroid nodule.

PLA cost

The current cost of a PLA treatment (including equipment, medical team, and disposable kits) is about 450 euros (c. US$550).

Conclusions

A single PLA session succeeded in inducing a significant and persistent nodule volume reduction in cold thyroid

nodules. The procedure was rapid, safe, and well tolerated and its effects were essentially predictable. Most treated patients reported an improvement in local symptoms, which was stable during a prolonged follow-up. PLA treatment was more effective than long-term LT4 therapy in inducing both nodule shrinkage and improvement in local symptoms. Clinical control with no active treatment, on the other hand, was associated with a high probability of further nodule growth and of the progression of local symptoms.

On the basis of these findings, PLA therapy should be considered for the mini-invasive debulking of benign cold nodules in patients with local pressure symptoms. The treatment should be performed only by well-trained operators and after a careful cytological evaluation.

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